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ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,962	ULLRICH ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2, 8 and 10-17* is/are pending in the application.

4a) Of the above claim(s) *11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,8,10 and 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/8/04* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 2, 8 and 10-17 are all the pending claims in this application.

2. Claims 1, 3-7 and 9 were cancelled, Claims 2, 8 and 10 were amended and new Claims 13-17 were added in the Response of 4/9/08.

3. Claims 11 and 12 are withdrawn from examination.

4. Claims 2, 8, 10 and 13-17 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for objection and rejection. This action is FINAL.

Information Disclosure Statement

6. The information disclosure statement filed 9/8/04 has been considered for the US patent references and the non-patent literature references only which have now been provided in the Response of 4/9/08. Copies of the international and foreign patent references have not been provided and thus have not been considered, and those references are stricken on the attached 1449 form.

Withdrawal of Objections

Specification

7. The objections to the specification are withdrawn for the following reasons:

a) The specification now provides a cross-reference to the priority documents for this application.

b) The Brief Description of the Drawings on p. 9 has been inserted between the Summary of the Invention and the Detailed Description of the Invention.

c) The Abstract of Disclosure is now a separate sheet to the specification.

d) The figure legends for Figures 1-7 now describe in brief but sufficient detail the data depicted in any of the figures.

Withdrawal of Rejections

Claim Rejections - 35 USC § 101

8. The rejection of Claims 1-4 and 8-10 for being directed to non-statutory subject matter (i.e., “use” claims) is withdrawn in view the cancelled claims and new method claims 13-17.

Claim Rejections - 35 USC § 112, second paragraph

9. The rejection of Claims 1-4 and 8-10 for reciting improper Markush group language: “selected from” is withdrawn and moot for cancelled claim 1.

10. The rejection of Clams 3 and 4 for the recitation “acts on” in Claim 3 is withdrawn and moot for the cancelled claims.

11. The rejection of Claim 8 in lacking antecedent basis for the limitation "the agent" is withdrawn in view of the amendment of Claim 8 to recite the “composition.”

12. The rejection of Claim 10 in lacking antecedent basis for the limitation "the cancer" is withdrawn in view of the amendment of the claim to depend from new claim 13.

Claim Rejections - 35 USC § 112, first paragraph

Enablement

13. The rejection of Claims 1-4 and 8-10 under 35 U.S.C. 112, first paragraph, in lacking enablement for the method is withdrawn and moot for cancelled independent Claim 1 and claims 3, 4, and 9.

The rejection is reinstated for new Claims 13-17 and dependent claims 2, 8 and 10 discussed below.

Claim Rejections - 35 USC § 102

14. The rejection of Claims 1-4 and 8-10 under 35 U.S.C. 102(b) as being anticipated by Prenzel et al. (Nature 402(6764):884-8 (1999)) is withdrawn and moot for the cancelled claims.

Prenzel does not disclose an antibody that both binds pro-HB-EGF and blocks processing of pro-HB-EGF.

15. The rejection of Claims 1-4 and 8-10 under 35 U.S.C. 102(b) as being anticipated by Freeman et al. (J. Cell. Biochem. 68:328-338 (1998)) is withdrawn and moot for the cancelled claims.

Freeman does not disclose an antibody that both binds pro-HB-EGF and blocks processing of pro-HB-EGF.

16. The rejection of Claims 1-4 and 8-10 under 35 U.S.C. 102(b) as being anticipated by Bevec [*Wallasch*] (WO 200135899; published May 25, 2001) is withdrawn and moot for the cancelled claims.

Wallasch does not disclose an antibody that both binds pro-HB-EGF and blocks processing of pro-HB-EGF.

Anti-HB-EGF Antibody inhibitor

17. The rejection of Claims 1-4, 8 and 9 under 35 U.S.C. 102(b) as being anticipated by Ito et al. (BBC 1310(1): 163-167 (1996); Abstract) is withdrawn and moot for the cancelled claims.

Ito does not disclose an antibody that both binds pro-HB-EGF and blocks processing of pro-HB-EGF.

18. The rejection of Claims 1-4 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Elder et al. (US 20020169176; published November 14, 2002; filed February 11, 2002) is withdrawn and moot for the cancelled claims.

Elder does not disclose an antibody that both binds pro-HB-EGF and blocks processing of pro-HB-EGF.

19. The rejection of Claims 1-4 and 8-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Hanke et al. (WO 200077195; published December 21, 2000) is withdrawn and moot for the cancelled claims.

Hanke does not disclose an antibody that both binds pro-HB-EGF and blocks processing of pro-HB-EGF.

New Grounds for Objection

Claim Objections

20. Claims 13 and 17 are objected to because of the following informalities: the claims recite an apparent typographical error for "a subject*ed* in need thereof" and should seemingly recite "a subject in need thereof." Appropriate correction is required.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 13 and 15 recite the limitation "the growth factor receptor". There is insufficient antecedent basis for this limitation in the claim.

b) Claim 15 recites the limitation "the EGFR family". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

22. Claims 2, 8, 10 and 13-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2, 8, 10 and 13-17 recite subject matter for “an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF” that is not defined in the specification (*In re Morris* 127 F.3d 1048, 44USPQ2d 1023 (Fed. Cir. 1997) and MPEP 2163).

The specification discloses “an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF.” The specification does not otherwise cite a commercial example(s) of such an antibody or reduce to practice any antibody meeting all of these properties. The prior art does not support the existence of any such antibody.

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001)), the claimed invention must meet the following criteria as set forth.

Actual reduction to practice: the specification does not show any embodiments that meet the limitations for "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF" reduced to practice.

Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the claimed invention as a whole (i.e., using the antibody to prevent or treat cancer).

Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the antibody.

Method of making the claimed invention: the specification does not teach or suggest how to make "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF".

Level of skill and knowledge in the art: the examiner's search of commercial literature databases (Medline, CAPLUS), the ATCC website and the ExactAntigen database did not reveal the existence of any "antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF."

Predictability in the Art: one of skill in the art could reasonably expect to generate an antibody that binds the pro-HB-EGF protein but it is not predictable that the antibody

would also inhibit processing of said pro-HG-EGF or that the same antibody could be administered in a subject and still exhibit the same properties.

Applicants' specification does not show the existence of a commercial antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF. Applicants' specification has not reduced to actual practice a working example of an antibody with these characteristics. One of skill in the art could reasonably conclude that Applicants were not in possession of "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF" at the time of application filing.

Enablement

23. Claims 2, 8, 10 and 13-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 13-16 and (dependent claims 2, 8 and 10) are interpreted as being drawn to a method for the prevention or treatment of cell proliferation, cell migration, invasivity or anti-apoptosis in any cancer, where the cancer is associated with increased G-protein mediated signal transduction and is colon, kidney, bladder, prostatic, breast, lung, or ovarian cancer and where the subject is administered a composition comprising an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF (Claim 13), where the antibody inhibits activation of a GFR of the EGFR family (Claim 14), and the GFR is HER-2, HER-3 or HER-4 (claim 15), where the method is for the treatment (Claim 16), where the GFR is EGFR (Claim 2), where the composition is a pharmaceutical composition comprising the antibody (Claim 8) and the cancer is a human cancer (Claim 10).

Claim 17 is interpreted as being drawn to a method for the treatment of cell proliferation, cell migration, invasivity or anti-apoptosis in any cancer, where the cancer is associated with increased G-protein mediated signal transduction and is colon, kidney, bladder, prostatic, breast, lung, or ovarian cancer and where the subject is administered a composition comprising an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF.

The relative skill in the art is a clinical oncologist.

Disclosure in the Specification

The specification contemplates using an antibody capable of binding to pro-HB-EGF and which inhibits processing of precursor as an embodiment for affecting a

growth-factor receptor ligand precursor. The specification contemplates using the antibody in order to treat *or* prevent a disorder associated with G-mediated signal transduction effecting EGFR where the agent effects a process of cell proliferation, cell migration, invasivity and/or anti-apoptosis. No where in the specification are any methods using an in vitro cell-based assay much less an animal model correlate for any disorder encompassed by the claims showing that the antibody could be practiced in the claimed method and that a prophylactic or therapeutic effect would be accomplished. One of skill in the art could not practice the invention because Applicants have not identified an example of an antibody having the instant claimed properties much less where the antibody is administered to any subject having any cancer. Applicants' prophetic antibody has the alleged properties of preventing just any cancer and treating just any cancer where the general field of art recognizes the unpredictability of preventing/treating just any cancer much less using an immunotherapeutic/ immunoprophylactic antibody in a human subject.

Prior Art Status: Cancer Treatment and Prevention is Unpredictable

A tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularization, perfusion and drug access to the tumor cells are not evenly distributed and this is an important source of heterogeneity in tumor response to drugs. Therefore, the antibody effect(s) in any cancer subject much less a human in the absence of any in vitro cell-based testing or in vivo animal cancer model correlates as in the present case, is not reliable or predictable and further evaluation in cell assays systems and animal tumor systems is essential.

Further, it is not clear what the best approaches are to examining a drug or antibody effect in preclinical testing. Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003); cited in the PTO 892 form of 1/9/08) conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006); cited in the PTO 892 form of 1/9/08) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in

humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar.

Cespedes et al. (Clin. Transl. Oncol. 8(5):318-329 (2006)) review the some of the examples of art-recognized animal disease model correlates for the corresponding human disease in Tables 1-3. Cespedes emphasizes the challenges in using animal models as predictive correlates for human responsiveness to therapeutics and sets forth on pp. 318-319 a list of criteria that would represent the ideal in vivo model for studying cancer therapeutics. As regards the use of xenograft modeling, Cespedes teaches:

> "One limitation of the xenograft models is precisely their use of an immunocompromised host, which eliminates the possibility of studying the role of the immune system in tumor progression. Some authors also think that cancer and host cells being from different species may limit the occurrence of critical tumor-stroma interactions, leading to an inefficient signaling. The organ of implantation could also become a limitation to the system. Thus, as it has already been described, subcutaneous xenografts infrequently metastasize and are unable to predict response to drugs" (p. 325, Col. 1, ¶2).

One skilled in the art would reasonably conclude that evidence obtained in in vitro cell-based assays or even mouse cancer models using the prophetic antibody of applicants invention would not even necessarily correlate with results expected in any human tumor.

Skill in the Art/Undue Experimentation

It appears that undue and inordinate experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification alone and the specification fails to enable the use of the method for any tumor therapy and any tumor prevention much less in any human. Due the unpredictability of cancer therapeutics in general, as evidenced by Voskoglou-Nomikos, Dennis and Cespedes, *and* in view of the absence of guidance for procuring or making an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF and the absence of working examples concerning the use the prophetic antibody in the method invention, one skilled in the art would not know how to practice the broadly claimed invention. One skilled in the art could not administer to any subject having any cancer "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF" for the treatment and/or prevention of any cancer much less a human cancer and its accompanying pathologies, without undue experimentation.

Conclusion

24. No claims are allowed.

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643